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U.S. Environmental Protection Agency
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U.S. Environmental Protection Agency
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Office of Solid Waste and Emergency Response
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

Both inhalation and oral estimates of interim accpetable intakes are provided for mixed xylenes, o-xylene and m-xylene. Sufficient data were not available to develop estimates for p-xylene.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with xylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Hazard Assessment Report on Xylene. Prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for the Environmental Criteria and Assessment Office, Research Triangle Park, NC.

U.S. EPA. 1985. Drinking Water Criteria Document for Xylenes. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. (Final draft)

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e. protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Inhalation data for mixed xylenes as well as the o-, m- and p-isomers are fragmented. Mixed xylenes and the o-isomer have been evaluated in subchronic studies with adult animals. All of these compounds have been evaluated in teratology studies. NOELs for fetotoxicity have been established for all isomers except p-xylene. Additional clarification of the lowest fetotoxicity effect level for mixed xylenes is needed. An inhalation AIS for o-xylene of 67 mg/day is estimated based on fetotoxicity. An AIS for m-xylene which is less fetotoxic is based on analogy to nonreproductive effects of o-xylene and is estimated as 71 mg/day. The AIS for mixed xylenes is based on a fetotoxicity NOEL and estimated to be 48 mg/day. No value is estimated for p-xylene. For chronic exposure, an AIC for o-xylene and by analogy, m-xylene is estimated as 14 mg/day based on a 1-year inhalation study in rats. For mixed xylenes an AIC of 28 mg/day is estimated based on a rat 90-day inhalation study. No AIC for inhalation is estimated for p-xylene.

Only one oral administration study was located. This study exposed rats to o-xylene by their diet for 6 months at one dose level and defined a LOAEL. Based on this study, an oral AIS of 7 mg/day and an oral AIC of 0.7 mg/day were estimated for o-xylene and by analogy for m- and mixed xylenes. An AIC was not estimated for p-xylene. A CS of 9 was calculated based on teratogenicity and fetotoxicity in mice at a level also associated with maternal toxicity.

These estimates, especially for the oral route, should be reviewed as additional data become available.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

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Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Services
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Xylene can exist in three isomeric forms. Commercial xylene is a mixture of three isomers in the following percent ranges: o-xylene, 10-25%; m-xylene, 45-70%; and p-xylene, 6-15% (NIOSH, 1975). The relevant physical and chemical properties of the individual xylenes and their environmental fate are as follows:

Chemical class	monocyclic aromatic hydrocarbon
CAS Registry No.	o-xlene, 95-47-6; m-xylene, 108-38-3 p-xylene, 106-42-3
Molecular weight	106.17
Vapor pressure in mm Hg at 20°C	o-xylene, 5; m-xylene, 6; p-xylene, 6.5 (Verschueren, 1983)
Water solubility in mg/ℓ at 25°C	o-xylene, 170.5; m-xylene, 146; p-xylene, 156 (Sutton and Calder, 1975)
Octanol/water partition coefficient	o-xylene, 589; m-xylene, 1585; p-xylene, 1413 (Leo et al., 1971)
BCF (estimated)	o-xylene, 45; m-xylene, 105; p-xylene, 95
Half-life in air:	o-xylene, 13 hours; m-xylene, 8 hours; p-xylene, 15 hours (Singh et al., 1981)
Half-life in water:	2.6-11 days for the three xylenes (estimated)

The BCFs for the three xylenes have been estimated by using the equation of Veith et al. (1979) and the octanol/water partition coefficient values stated above.

The dominant process for the removal of xylenes from water is volatilization (U.S. EPA, 1985). The half-lives for the three xylenes are based on an EXAMS model because of evaporation (Burns et al., 1981), with the appropriate input parameter given in U.S. EPA (1985).

The half-lives for the three xylenes in soil could not be located in the available literature; however, based upon the characteristics of their evaporation from water, volatilization is expected to be the predominant loss mechanism from the soil surface. In subsurface soil, biodegradation of xylenes is likely to be a slow process (U.S. EPA, 1985). The persistence of xylenes in soils has been reported to be $\geq$6 months (NRC, 1980). Therefore, in subsurface soils with low organic carbon content, xylenes may infiltrate into groundwater from soil (U.S. EPA, 1985).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although explicit data regarding the absorption of xylenes from the gastrointestinal tract of animals or humans were not located, it can be inferred that absorption by this route is nearly complete. In the rabbit, 85-90% of an administered oral dose of xylene isomers (ranging from 0.9-1.7 g/animal) was accounted for in the urine, while pulmonary excretion may have accounted for the remaining xylene (Bray et al., 1949).

2.2. INHALATION

Studies evaluating the inhalation absorption rate in humans exposed to doses ranging from 100-1300 mg/m^3 indicated that ~60% of the xylene present in the inspired air, regardless of the isomer or isomer mixture used, is absorbed (Astrand et al., 1978; Riihimaki et al., 1979a; Sedivec and Flek, 1974, 1976; Gamberale et al., 1978; Se'nczuk and Orlowski, 1978). Exercise increases the relative amount of xylene absorbed (Astrand et al., 1978; Riihimaki et al., 1979b).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

Table 3-1 summarizes experiments regarding subchronic xylene exposure.

3.1.1. Oral. The only animal study of subchronic oral exposure to xylene was performed by Bowers et al. (1982). Twenty male Long-Evans rats weighing 0.8-0.9 kg were fed xylene at a dose of 200 mg/kg of food (200 ppm). Groups of five animals were killed after 1, 2, 3 and 6 months. The livers were grossly normal, but two types of vesicles were seen with the transmission electron microscope in the hepatocytes of the xylene-treated animals. These vesicles were not present in the control group. The authors (Bowers et al., 1982) noted that the vesicles were involved in the elimination of xylene or its metabolites or both. The purpose of one type of vesicle may have been to increase the surface area of hepatocytes. The focus of this experiment seemed to be exclusively on the liver; no other effects were reported.

3.1.2. Inhalation. Although Ungvary et al. (1981) presented some evidence in acute toxicity studies that females may be more sensitive to xylene exposure than males, most of the subchronic inhalation studies have been done on males (Carpenter et al., 1975; Jenkins et al., 1970; Savolainen et al., 1979). Male rats were exposed to mixed xylenes (p-xylene, 8%; m-xylene, 65%; o-xylene, 8%; ethylbenzene, 19%) at a dose of 180, 460 and 810 ppm (770, 2000 and 3500 mg/m^3, respectively) for 6 hours/day, 5 days/week for 13 weeks (Carpenter et al., 1975). There were 25 rats in each group. No biochemical effects (blood levels of urea, nitrogen, glutamic oxalacetic transaminase, glutamic pyruvic transaminase and alkaline phosphatase) or histological effects (lung, liver, kidney, brain, pituitary, trachea, thyroid, parathyroid, heart, spleen, gastrointestinal tract, muscle, nerve and bone marrow) were seen in rats treated at the two lower

TABLE 3-1

Subchronic Exposure to Xylene

Route	Dose	Exposure	Species	Sex	Number	Effect	Reference
Oral	200 mg/kg	1, 2, 3 and 6 months	Long-Evans rats (0.8-0.9 kg)	M	20	Livers were grossly normal; ultra-structurally, vesicles were present.	Bowers et al., 1982
Inhalation	180 ppm (770 mg/m³) 460 ppm (2000 mg/m³) 810 ppm (3500 mg/m³)	6 hours/day, 5 days/week, 13 weeks	rats	M M M	25 25 25	No effects were seen biochemically or histologically at 180 or 460 ppm. Transitory changes in blood cell counts and slight changes in renal tubules at 810 ppm.	Carpenter et al., 1975
Inhalation	180 ppm (770 mg/m³) 460 ppm (2000 mg/m³) 810 ppm (3500 mg/m³)	6 hours/day, 5 days/week, 13 weeks	dogs	M M M	4 4 4	No effect on blood cell counts, clinical chemistry, body weight, liver and kidney weights.	
Inhalation	78 ppm (337 mg/m³)	continuous for 90 days	rats guinea pigs dogs monkeys	M/F M/F M	14 15 2 3	No effect on hematology or body weight gain.	Jenkins et al., 1970

dose levels. In rats exposed to xylene at the highest dose level, there was an increase in erythrocyte and monocyte counts after 3 weeks of xylene inhalation, which disappeared during weeks 7-13 of the experiment. The authors did not consider this an adverse effect (Carpenter et al., 1975). Male dogs were exposed to mixed xylenes at concentrations of 180, 460 or 810 ppm (770, 2000 and 3500 mg/m^3, respectively) for 6 hours/day, 5 days/week for 13 weeks (Carpenter et al., 1975). There were four dogs in each group. No effect on blood cell count, clinical chemistry, urinalysis, body weight or liver and kidney weight was reported.

In another study, 20 male Wistar rats were exposed to 300 ppm (1300 mg/m^3) xylene for 6 hours/day, 5 days/week for <18 weeks (Savolainen et al., 1979). Some rats were killed at 5, 9, 14 and 18 weeks. Brain superoxide dismutase decreased after 5 weeks of xylene exposure, but increased after 18 weeks of xylene exposure. Brain cytosolic glutathione peroxidase activity was significantly decreased after 14 weeks, but was not significantly different from control levels after 18 weeks of xylene exposure. Some behavioral changes (decreased preening and reduced activity) were seen in the xylene-treated rats (Savolainen et al., 1979).

Jenkins et al. (1970) exposed NMRI:O(SD) Sprague-Dawley or NMRI:(LE) Long-Evans derived rats (apparently mixed strains and sexes), NMRI:(ASH) Princeton derived guinea pigs (mixed sexes), squirrel monkeys and beagle dogs to o-xylene (purity not specified) for either 30 intermittent exposures (8 hours/day, 5 days/week) or continuously for 90 days. Group sizes were: 12 rats in the intermittent protocol, 14 rats in the continuous protocol, 15 guinea pigs for each exposure condition, 2 male dogs for each exposure condition, 2 male monkeys on the intermittent protocol and 3 exposed continuously. Exposure concentrations were: 3358 mg/m^3 for the intermittent

protocol and 337 mg/m³ for the continuous protocol. Blood counts, hemoglobin and hematocrit were monitored in addition to body weight. Histopathological evaluation was conducted on heart, lung, liver, spleen and kidney of all species at the end of exposure and brain and spinal cord from dogs and monkeys.

Apparently statistics were not run on body weights. Rats continuously exposed gained more weight than controls. Guinea pigs and dogs also gained more weight on the contiuous protocol than did controls. Both control and exposed dogs lost equal amounts of weight. Statistics were not reported for blood chemistries, but none of the values appeared different. Histopathology apparently yielded negative results although data were not shown. Organ weights were not reported. Two rats died on the third exposure day and both a rat and a monkey died on day 7 on the intermittent protocol, while one rat died on day 56 of the continuous protocol. If necropsies were done the results were not reported, making it impossible to ascertain whether the deaths were treatment related.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic oral toxicity of xylene could not be located in the available literature.

3.2.2. Inhalation. Male CFY rats were exposed to 4750 mg/m³ of xylene for 8 hours/day, 7 days/week for 1 year (Tatrai et al., 1981). Although the xylene-exposed animals ate more, they had decreased body weights. Xylene-exposed rats also had hepatomegaly and an altered hepatic enzyme pattern. Cytochrome P-450, NADPH-cytochrome c reductase, aniline hydroxylase and aminopyrin-N-demethylase activity were increased, while bromosulfophthalein retention time in the liver was decreased. Ultrastructurally, the centrilobular hepatocytes of xylene-treated rats had moderate smooth endoplasmic

reticulum proliferation, an increased number of peroxisomes and autophagous bodies, glycogen depletion and, occasionally, damaged mitochondria. Proliferation of the smooth endoplasmic reticulum has been correlated with increased mixed function oxidase activity. Liver enlargement was attributed to functinal hypertrophy.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Oral exposure to 3.10 or 4.13 g/kg/day on days 6-15 of gestation was toxic to pregnant CD-1 mice, producing a mortality incidence of 12/38 at 3.10 g/kg/day (Marks et al., 1982). Doses of 2.06 and 2.58 g/kg/day caused increased resorptions and fetal malformations, and decreased fetal body weights (Marks et al., 1982). Doses of 1.03 and 0.52 g/kg/day had no apparent effects on fetal or maternal toxicity.

3.3.2. Inhalation. Shigeta et al. (1983) reported that IRC mice exposed to 500, 1000, 2000 or 4000 ppm xylene for 6 hours/day on days 6-12 of gestation did not differ from controls in the number of implantation sites or the number of resorbed or dead fetuses. At dose levels of 2000 and 4000 ppm, fetal weights were decreased and skeletal ossification was delayed.

Continuous exposure of 26 pregnant CF4 rats to 1000 mg/m³ mixed xylenes (10% o-xylene, 50% m-xylene, 20% p-xylene, 20% ethylbenzene) on days 9-14 of gestation resulted in an increased incidence of fused sternebrae and extra ribs in the offspring. The incidence of retarded skeletal development appeared higher but was not significantly different (Hudak and Ungvary, 1978). There was no effect on maternal weight gain, mean litter size, mean placental weight, mean fetal weight, fetal resorption or fetal mortality.

Pregnant CF4 rats were exposed to 150, 1500 or 3000 mg/m³ of each of the isomers of xylene continuously on days 7-14 of gestation (Ungvary et al., 1980). The number of rats in each exposed group was 20 except for the

3000 mg/m³ m-xylene group which contained 30 rats. Groups of 15, 25 or 20 rats served as controls for the o-, m- and p-isomers, respectively. Signs of maternal toxicity included decreased food consumption in all 3000 mg/m³ groups and in the 1500 mg/m³ o-xylene-exposed group. The 3000 mg/m³ group exposed to m-xylene exhibited increased mortality (4/30). The authors state that maternal weight gain decreased as a function of exposure concentration during the early days of exposure (data not shown). The only significant effect on weight gain by day 21 of gestation was in the m-xylene group exposed to 3000 mg/m³. An increase in maternal liver:body weight ratio was reported for all o-xylene exposed groups. Dams exposed to p-xylene at all dose levels had significantly lower placental weights.

Litters from dams exposed to p-xylene at 3000 mg/m³ showed significantly increased fetal loss (69% vs. 4% in controls). The number of rats pregnant was decreased in dams exposed to 3000 mg/m³ of o-xylene or m-xylene. The average number of implants per rat was decreased in the group exposed to m-xylene at 3000 mg/m³.

Mean fetal weight was significantly reduced following exposure to all three isomers at the 3000 mg/m³ concentration. Additionally, exposure to o-xylene at 1500 mg/m³ resulted in significant fetal weight reductions. There were no indications of increased incidence of external, soft tissue or skeletal malformations. An increase in the incidence of extra ribs, classified by the authors as a skeletal anomaly, was seen in litters from dams exposed to 3000 mg/m³ of either m-xylene or p-xylene. Skeletal retardation occurred in fetuses from dams exposed to 3000 mg/m³ o-xylene and in all p-xylene-exposed groups.

In addition, the number of alkaline phosphatase positive proximal convoluted tubules as well as the number and intensity of the positive staining nephrons for succinic dehydrogenase, acid phosphatase and glucose-6-phosphatase was reduced in the o- and p-xylene fetuses from dams exposed to 3000 mg/m³. In the liver and thymus cells from fetuses of dams exposed to all three isomers at 3000 mg/m³ there was a decrease in succinic dehydrogenase and glucose-6-phosphatase activities. The enzyme changes in the kidneys were interpreted by the authors as an indication of a delay in maturation.

In summary, exposure to 1500 mg/m³ produced no adverse effects on litters exposed to m-xylene, 150 mg/m³ produced no adverse effects on litters exposed to o-xylene, and p-xylene resulted in fetotoxicity as evident by delays in skeletal ossification following exposure to the lowest concentration tested (150 mg/m³).

Charles River CD female rats were exposed to mixed xylenes (11% o-xylene, 52% m-xylene, 0.31% p-xylene, 36.1% ethylbenzene) at concentrations of 0, 433 and 1733 mg/m³ on days 6 through 15 of gestation, 6 hours/day (Litton Bionetics, 1978). There were 25 pregnant dams per exposure group. Animals were sacrificed on day 20 of gestation. The number of implantation sites, resorption sites, live and dead fetuses, fetal weights and external abnormalities were recorded. One-third of the fetuses from each litter were examined for soft-tissue anomalies, with the remainder examined for skeletal abnormalities. The only effect apparent was a significant increase in the number of offspring with "unusual skeletal variations". Incidences of fetuses were 19 in the control, 24 in the low-dose group and 37 in the high-dose group; however, the number of litters affected were 9, 6 and 10. The authors did not judge this effect to be

treatment related because the majority of the affected fetuses were from three litters and because all fetuses from these litters were "small".

3.4. TOXICANT INTERACTIONS

The interaction of xylene with ethanol (Savolainen et al., 1978; Elovaara et al., 1980; Savolainen and Riihimaki, 1981; Seppalainen et al., 1981; Riihimaki et al., 1982a,b), 1,1,1-trichloroethane (Savolainen et al., 1982) and carbon tetrachloride (Tatrai et al., 1979) have been studied. In rats, oral ingestion of alcohol (15% of drinking fluid) potentiates the effect of inhalation exposure to 300 ppm of xylene given 6 hours/day, 5 days/week (Savolainen et al., 1978; Elovaara et al., 1980). After 2 weeks of simultaneous exposure, changes in hepatic and renal enzyme activities (7-ethoxycoumarin, o-deethylase, UDP-glucuronosyltransferase and cytochrome P-450) were noted. After 18 weeks of exposure, increased numbers of intracellular lipid droplets were present in the livers of rats exposed to both xylene and ethanol, but were absent from the livers of rats exposed to xylene or ethanol separately. In humans, alcohol ingestion (0.8 g/kg), in conjuncton with xylene exposure (290 ppm for 4 hours), increased the effect of alcohol on central equilibrium control mechanisms (Savolainen and Riihimaki, 1981). Xylene doubled the volume of centrilobular liver necrosis caused by ingestion of 2 mℓ/kg bw of carbon tetrachloride in rats (Tatrai et al., 1979). Xylene and 1,1,1-trichloroethane each depressed the metabolism of the other in humans, but no histopathological effects were described (Savolainen et al., 1982).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the human carcinogenicity of xylene could not be located in the available literature.

4.2. BIOASSAYS

A bioassay of the carcinogenicity of xylene is being conducted on rats and mice orally exposed to xylene (NTP, 1983), but a complete and final report of the study is not available at this time.

4.3. OTHER RELEVANT DATA

m-Xylene, p-xylene and o-xylene were not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence or absence of the rat liver microsomal fraction (Florin et al., 1980; Bos et al., 1981). Mixed xylenes were not mutagenic in Escherichia coli strains WP2, WP2uvrA, CM611, WP67, WP100, W3110 and p3478 (McCarroll et al., 1981). Xylene was not mutagenic in the Drosophila recessive lethal test (Donner et al., 1980), and did not increase chromosomal aberrations in hematopoietic cells (Donner et al., 1980) or SCEs in human lymphocytes in vitro (Gerner-Smidt and Friedrich, 1978).

4.4. WEIGHT OF EVIDENCE

The results of the NTP (1983) bioassay are not available, but it should be noted that tumors were not observed in rats that were exposed to xylene vapor (4750 mg/m^3) for 1 year (Tatrai et al., 1981). IARC has not evaluated the risk to humans associated with oral or inhalation exposures to xylene. Using the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), xylene is most appropriately designated as a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1983) recommends a TWA-TLV of 100 ppm (435 mg/m^3) and a STEL-TLV of 150 ppm (655 mg/m^3). NIOSH (1975) recommends a 10-minute ceiling of 200 ppm xylene because the attention, judgment and perception of the worker can be altered due to the depressant effect of xylene on the CNS. OSHA (Code of Federal Regulations, 1981) has promulgated a TWA limit of 100 ppm for occupational exposure to xylene.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. In the only study (Bowers et al., 1982) on oral exposure to xylene one dietary level (200 ppm) of o-xylene was given to 20 male Long-Evans rats. Groups of five rats were killed after 1, 2, 3 and 6 months of o-xylene exposure. No gross or light microscopic effects were seen; however, 200 ppm appeared to be a NOAEL because ultrastructural changes in liver morphology, which did not appear to be adverse, were noted. Assuming a rat consumes 5% of its body weight per day, the estimated NOAEL from this study is 10 mg/kg/day. Applying an uncertainty factor of 100 results in an estimated AIS of 7 mg/day for a 70 kg human. This study is flawed by small group sizes and the use of only one exposure level. However, the effects observed are consistent with those following inhalation exposure to o-xylene. Tatrai et al. (1981) exposed male rats to 4750 mg/m^3 o-xylene 8 hours/day, 7 days/week for 1 year. Effects noted included decreased body weights, minimal liver damage apparent only following electron microscopy and hepatomegaly attributed to functional hypertrophy. For purposes of comparison a dose may be estimated from this inhalation study. Assuming rats breath 0.223 m^3/24 hours, weigh 0.35 kg and that 50% of the inhaled xylene is absorbed (U.S. EPA, 1985), the following dose is estimated: 4750 mg/m^3 x 0.223 m^3/24 hours x 8/24 hours x 0.50 ÷ 0.35 = 504 mg/kg. Applying an uncertainty factor of 1000 (10 to estimate a NOAEL from a LOAEL, 10 for interspecies extrapolation, and 10 for interindividual variability) results in an alternate AIS estimate of 35 mg/day. This estimate is within a factor of 5 of the estimate derived from the Bowers et al. (1982) study. As a result of the inherent uncertainty in route to route extrapolation, the more conservative estimate of 7 mg/day based on the oral data is proposed as

the AIS for o-xylene. This value should be reevaluated when more complete oral data become available.

Jenkins et al. (1970) conducted an additional inhalation evaluation of o-xylene in rats, monkeys and dogs either as 3358 mg/m^3 8 hours/day, 5 days/week for 30 exposures or 389 mg/m^3 continuously for 90 days. Unexplained deaths in rats preclude use of the intermittent exposure data. Organ weights were not reported and apparently electron microscopic evaluations of livers were not conducted. Pathology data were reported as a single sentence which stated results were essentially negative. This study would suggest an AIS of 87 mg/day. However, the protocol as reported suggests that subtle liver effects documented by Bowers et al. (1982) and Tatrai et al. (1981) could have been missed. Therefore, this study is not recommended as a basis for quantitative risk assessment.

Data are not available for oral exposure of adult animals to commercial mixed xylenes nor for the m- or p-isomers. An oral teratology evaluation of mixed xylenes in mice indicated no effects on offspring at doses $\leq$1.03 g/kg/day. Acute toxicities of the three isomers and commercial mixed xylenes are similar (U.S. EPA, 1985). In the absence of additional experimental data it may be appropriate to apply the AIS for o-xylene to mixed xylenes and m-xylene. The p-isomer is the most severely fetotoxic of the xylenes in rat teratology studies by inhalation and the only isomer for which a NOEL for fetotoxicity has not been established. Although xylene appears to exhibit a greater potential for fetotoxicity by the inhalation route, the oral evaluation was conducted with mice and the inhalation evaluations with rats; thus complicating interpretations. Until these questions are resolved it is suggested that the o-xylene based AIS may not be appropriate for the p-xylene isomer.

6.1.2. Inhalation. As discussed in Section 6.1.1. a 1-year evaluation of the toxicity of inhaled o-xylene has been conducted (Tatrai et al., 1981). This study is considered more appropriate for assessment of adult inhalation toxicity than Jenkins et al. (1970) as discussed in Section 6.1.1. In addition, an inhalation teratology study has been conducted in rats which defined a NOEL for fetotoxicity of 96 mg/kg (extrapolated from an exposure concentration of 150 mg/m^3) (Ungvary et al., 1980). The LOAEL from Tatrai et al. (1981) is estimated to be 1009 mg/kg, estimated as in Section 6.1.1. with the omission of the absorption factor which was applied to estimate absorbed dose for purposes of route:route extrapolation. Applying an uncertainty factor of 10 to estimate a NOAEL from a LOAEL results in an estimated NOAEL of 101 mg/kg/day, essentially the same as the fetotoxicity NOEL of 96 mg/kg/day. Using the NOEL for the most sensitive endpoint, fetotoxicity, results in an estimated inhalation AIS of o-xylene of 67.2 mg/day [96 mg/kg/day ÷ 100 (uncertainty factor) x 70 kg].

m-Xylene was less fetotoxic than o-xylene with a NOEL of 956 mg/kg/day (exposure concentration 1500 mg/m^3). Therefore, for m-xylene the LOAEL of 1009 from Tatrai et al. (1981) represents the lowest LOAEL assuming that the o- and m-isomers exhibit comparable toxicities. Applying an uncertainty factor of 1000 (10 to estimate a NOAEL, 10 for interspecies extrapolation and 10 for interindividual variability) results in an AIS of 70.7 that is essentially indistinguishable from the value based on fetotoxicity.

For mixed xylenes, Ungvary et al. (1980) established a fetotoxicity FEL of 637 mg/kg. Litton Bionetics (1978) established a NOAEL/LOAEL of 276 mg/kg/day based on increased numbers of fetuses, but not litters with skeletal abnormalities. The lower exposure concentration in the Litton Bionetics study clearly defined a NOEL of 69 mg/kg/day. Carpenter et al.

(1975) exposed male rats to 770, 2000 or 3500 mg/m³, 6 hours/day, 5 days/week. The highest exposure level appeared to represent a NOAEL. The estimated dose is 398 mg/kg. This dose is higher than the LOAEL/NOAEL for fetotoxicity in the Litton Bionetics (1978) study. Although the effect at this dose level was questionable, skeletal abnormalities are the endpoints observed following higher levels of xylene exposure. It is suggested that mixed xylenes be reevaluated for inhalation teratology utilizing doses around this possible threshold level. As an interim approach, the dose of 276 mg/kg will be considered a LOAEL. As a result, the NOEL for fetotoxicity of 69 mg/kg/day may be used to estimated an AIS. Dividing by an uncertainty factor of 100 and multiplying by 70 kg results in an estimated AIS for mixed xylenes of 48.3 mg/day.

A fetotoxicity NOEL for p-xylene has not been established. Significant fetotoxicity was seen at the lowest exposure concentration, 150 mg/m³ (96 mg/kg) (Ungvary et al., 1980). Since this dose is similar to the estimated NOAEL for other endpoints, an AIS for p-xylene is not proposed.

In conclusion, an AIS for o-xylene of 67 mg/day is proposed based upon fetotoxicity, and an AIS of 70.7 mg/day for mixed xylenes and m-xylene, while an AIS is not suggested for p-xylene. These values should be reevaluated when additional data become available.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Although pertinent data regarding chronic oral exposure to xylenes were not located in the available literature, an AIC for oral exposure of 0.7 mg/day can be derived from the AIS for oral exposure by dividing the AIS (7 mg/day) by an uncertainty factor of 10, applied to reflect the unknowns involved in extrapolating from subchronic to chronic expsoure. As described in Section 6.1.1., this value is suggested for mixed xylenes,

o-xylene and m-xylene, but not p-xylene. This AIC is substantially lower than that derived from the TLV (161 mg/day) using an uncertainty factor of 10 or that derived from an inhalation study in many species (4.43) (U.S. EPA, 1985). Both of these latter ADIs involve route-to-route extrapolation with its inherent uncertainties.

An RQ was derived for the teratogenicity (cleft palates) and fetotoxicity observed in mice treated by gavage with a mixture of xylenes and ethylbenzene at 2.58 g/kg/day on days 6-15 of gestation. A human MED is calculated by multiplying the animal dose by the cube root of the ratio of the body weight of mice (assumed: 0.03 kg) to that of humans (assumed: 70 kg) and multiplying the result by 70 to express the MED in mg/day for a 70 kg human. A human MED of 13616 mg/day, corresponding to an RV_d of 1, is calculated. Teratogenicity in the presence of maternal toxicity is assigned an RV_e of 9. A CS of 9 is calculated as the product of the RV_d and RV_e.

6.2.2. Inhalation. In the only subchronic inhalation study on o-xylene (Tatrai et al., 1981) considered adequate for risk assessment (see Section 6.1.2.), rats were exposed to one dose level of xylene (4750 mg/m³) for 1 year. This exposure level produced signs of toxicity, such as changes in body and organ weights, ultrastructural alterations and enzyme induction, without producing gross changes in the morbidity or mortality of the animals, and is considered to be a LOAEL. An AIS of 70.7 mg/day was estimated as described in Section 6.1.2. Applying an additional uncertainty factor of 5 to account for the duration of the study results in an estimated AIC of 14.1 mg/day. As outlined in Section 6.1.2., this AIS is proposed for o-xylene and by analogy to m-xylene. Carpenter et al. (1975) defined an inhalation subchronic NOAEL of 398 mg/kg for mixed xylenes. Applying an

uncertainty factor of 1000 and multiplying by 70 kg results in an estimated AIC of 27.9 mg/day. An AIC is not estimated for p-xylene. This value is lower than an estimate based on the TLV. (This estimate using an uncertainty factor of 10 would be 310 mg/day.)

6.3. CARCINOGENIC POTENCY (q_1^*)

Derivation of a q_1^* is precluded by the lack of carcinogenicity data. An NCI gavage study has been completed in rats and mice using a commercial mixture of xylene but the first draft of this report is not yet available (May, 1985).

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APPENDIX

Summary Table for Xylene

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS					
o-xylene	rat	150 mg/m³	fetotoxicity NOEL	67.2 mg/day	Ungvary et al., 1980
m-xylene	rat	4750 mg/m³ 8 hours/day	hepatomegaly weight loss	70.7 mg/day	Tatrai et al., 1981
mixed xylenes	rat	433 mg/m³ 6 hours/day	fetotoxicity NOEL	48.3 mg/day	Litton Bionetics, 1978
p-xylene	NA	NA	NA	ND	NA
AIC					
o-xylene	rat	4750 mg/m³ 8 hours/day	hepatomegaly weight loss	14.1 mg/day	Tatrai et al., 1981
m-xylene	rat	4750 mg/m³ 8 hours/day	hepatomegaly weight loss	14.1 mg/day	Tatrai et al., 1981
mixed xylenes	rat	3500 mg/m³ 6 hours/day	transient blood alterations	27.9 mg/day	Carpenter et al., 1975
p-xylenes	NA	NA	NA	ND	NA

APPENDIX (cont.)

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Oral					
AIS					
o-, m- and mixed xylenes	rat	200 ppm food	ultrastructural liver changes	7 mg/day	Bower et al., 1982
p-xylene	NA	NA	NA	ND	NA
AIC					
o-, m- and mixed xylenes	rat	200 ppm food	ultrastructural liver changes	0.7 mg/day	Bowers et al., 1982
p-xylene	NA	NA	NA	ND	NA

NA = Not applicable; ND = not derived